REMARKS

The present application was filed on July 27, 2001, with 54 claims: method claims 1-50 and composition claims 51-54. On December 5, 2001, the Office mailed a Restriction Requirement and Species Election. On January 7, 2002, Applicants elected the claims of Group I (claims 1-45 and 50) and the species dihydrotestosterone (DHT) propionate (including 4-dihydrotestosterone proprionate, 5α-dihydrotestosterone proprionate, and stanolone). The claims of Group I reading on the elected species were identified as claims 1-12, 16-18, 20-45 and 50.

In the first Office Action, all claims were rejected over Adams et al. (WO 99/66909) in view of Place et al. (U.S. Patent No. 5,877,216).

In the first Amendment, the subject matter of claim 40 was incorporated into claim 1 and claims 40-42 were canceled as were non-elected claims 51-54. Claim 55 was also added to the application. After entry of the Amendment, claims 1-39, 43-50, and 55 were pending.

In the Office Action under reply, claims 1-12, 16-18, 20-39, 43-45, 50, and 55 were considered. Claims 13-15, 19, were withdrawn from consideration as drawn to a non-elected species and claim 46-49 were withdrawn from consideration as drawn to a non-elected invention. The Examiner objected to the following language from claim 1: the acronym "SARMs" and the phrase "other peptidyl drugs." Claims 1-12, 16-18, 20-39, 43-45, and 55 were again rejected under 35 U.S.C. § 103(a) as obvious over Adams et al. in view of Place et al.

The Examiner's rejection is addressed in part by the amendments to the claims and are otherwise traversed for the reasons set forth below.

THE AMENDMENTS TO THE CLAIMS AND SPECIFICATION

A minor amendment has been made to the specification to remove the second incidence of the word "chlorpromazine" from the listing of dopamine antagonists in the paragraph bridging pages 16-17. Accordingly, no new matter has been added to the specification with the amendment.

Non-elected claims 46-49 have been canceled. Claim 55 has also been canceled.

Claim 1 has been amended to: (i) delete the acronym "SARMs"; (ii) replace the objected-to language "other peptidyl drugs" with --cytokines--; (iii) remove "vasoactive agents," "serotonin agonists," and "calcium channel blockers" from the scope of the claim; (iv) remove the word "optionally" before the recitation of the secondary active agents; and (v) add dopamine antagonists to the scope of the claim. Support for the recitation of the cytokines is found in the specification at page 15, line 1. Support for the addition of the dopamine antagonists is found in the specification at *inter alia*, page 11, line 6, and page 17, lines 1-4.

With the deletion of the word "optionally" before the recitation of the second active agent in claim 1, claim 25 has been canceled as redundant and claims 26-28 have been amended to depend from claim 1 rather than from claim 25.

New claims 56-58 and 60 recite the oral administration of: (a) an orally active androgenic agent as a first active agent; (b) a dopamine agonist or serotonin agonist as a secondary active agent; and (c) a vasodilator as a third active agent. Support for the oral administration of one or more secondary active agents, is found in the specification at *inter alia*, page 10, lines 24-25; page 17, lines 28-30; and page 22, lines 26-27. Support for the listing of dopamine agonists (claim 57) is found in the specification at *inter alia*, page 16, lines 29-30. Support for the listing of serotonin agonists (claim 58) is found in the specification at *inter alia*, page 15, line 29 to page 16, line 3. Support for the calcium channel blocker (claim 60) as a vasoactive agent is found in the specification at page 12, lines 12-15.

New claims 59 and 61 recite the oral administration of an androgenic agent as a first active agent and the oral administration of a vasoactive agent as a secondary active agent. Support for the oral administration of the vasoactive agent is set forth above. Because claim 59 recites a vasoactive agent as a second active agent, claim 29 has been canceled as redundant. With the cancellation of claim 29, claim 30 has been amended to depend from claim 59 rather than claim 29.

As all claim amendments and new claims are fully supported, no new matter has been added to the application.

CLAIM REJECTIONS - 35 U.S.C. § 103(a)

Claims 1-12, 16-18, 20-39, 43-45, and 55 stand rejected under 35 U.S.C. § 103(a) as obvious over Adams et al. in view of Place et al. This rejection is moot for canceled claims 25, 29, and 55 and is respectfully traversed for the remaining pending claims.

The independent claims of the present invention are claims 1, 44, 50, 56, and 59.

Claim 1 is drawn to a method for treating sexual dysfunction in a female mammal comprising the co-administration of an orally active androgenic agent with any one of the following compounds, alone or in combination, on an as-needed basis: a rho kinase inhibitor, a melanocortin peptide, an endothelin antagonist, a growth factor, a cytokine, a selective androgen receptor modulator, a neuropeptide, an amino acid, a serotonin antagonist, a dopamine antagonist, a potassium channel opener, a potassium channel blocker, and a non-androgenic steroid.

Claim 44 is drawn to a method for enhancing sexual desire and responsiveness in a female individual, comprising orally administering to the individual, approximately 0.25 to 72 hours prior to sexual activity, a therapeutically effective amount of an orally active androgenic agent, followed by

topical administration, approximately 0.25 to 24 hours prior to sexual activity, of a therapeutically effective amount of a prostaglandin.

Claim 50 is drawn to a method for enhancing sexual desire and responsiveness in a female individual, comprising orally administering an orally active androgenic agent to the individual in an amount effective to provide a blood level of the agent or a metabolite thereof that approximates the blood level of the agent or a metabolite thereof during ovulation, wherein said administering is carried out on an as-needed basis.

Claim 56 is drawn to a method for enhancing sexual desire and responsiveness in a female individual, comprising orally administering to the individual a therapeutically effective amount of: (a) an orally active androgenic agent as a first active agent; (b) a second active agent selected from a dopamine agonist and a serotonin agonist, and (c) a vasoactive agent as a third active agent, wherein administration is on an as-needed basis.

Claim 59 is drawn to method for enhancing sexual desire and responsiveness in a female individual, comprising orally administering to the individual a therapeutically effective amount of: (a) an orally active androgenic agent as a first active agent; and (b) a vasoactive agent as a second active agent, wherein administration is on an as-needed basis.

The primary reference, Adams et al., teaches a method for treating or ameliorating sexual dysfunction in female mammals by administering to a mammal in need of such treatment, a therapeutically effective amount of a compound that acts upon mid-brain pathways to increase blood flow to the ilio-hypogastric-pudendal arterial bed and genitalia (page 7, lines 18-23). The selected compound of Adams et al. is one that acts upon any of the mid-brain pathways, i.e., the dopaminergic, serotonergic, oxytocinergic, or nitroxidergic mid-brain pathways (page 8, lines 4-7).

Adams et al. discloses dopaminergic pathway compounds to include dopamine receptor ***agonists*** such as apomorphine, bromocriptine, lisuride, methergoline, pergolide, piribidil, and quinpirole (page 14, lines 6-8). The disclosed serotonergic pathway compounds include serotonin receptor ***agonists*** such as 1-(2,5,-dimethoxy-4-iodophenyl)-l-aminopropane, 5-methoxytrytamine, a-methyl-5-hydroxytryptamine, 2-methyl-5-hydroxytryptamin, N-acetyl- 5-hydroxytryptamine buspirone, and sumatriptin (page 14, lines 9-13). On this matter, it is noted that because Adams et al. expressly excludes dopamine and serotonin receptor ***antagonists*** from the disclosed compounds, these compounds are excluded from the scope of Adams et al. as compounds that act upon mid-brain pathways to increase blood flow to the ilio-hypogastric-pudendal arterial bed and genitalia. *See, e.g., Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991) (the inventor must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the

invention). Disclosed oxytocinergic pathway compounds include oxytocin, analogues such as isotocin, carnetocin, Lys-conopressin, deaminooxytocin, mesotocin, antocin, glymitocin, aspargitocin, valitocin, asvatocin, phasvatocin, and seritocin (page 14, lines 14-18). Adams et al. provides no examples of nitroxidergic pathway compounds. The preferred compound of Adams et al. is the dopamine receptor agonist, apomorphine (page 14, lines 19-20); the description of the embodiments of the invention relate exclusively to this compound.

Adams et al. teaches that the apomorphine may be administered in an ***oral*** dosage form (page 18, lines 7-11) and that an androgenic agent may be optionally co-administered with the apomorphine to potentiate the effects of the apomorphine (page 9, lines 10-14; page 17, lines 24-28). Adams et al. discloses suitable androgens for administration with the apomorphine to include testosterone, dihydrotestosterone (DHT), dehydroepiandrostenedione (DHEA) (page 20, lines 10-15). The androgenic agent may be administered orally or directly to mucosal tissue by way of rectal, vaginal, intranasal, buccal, or sublingual application (page 21, lines 13-25).

The secondary reference, Place et al., teaches a method for treating sexual dysfunction in a female individual through local administration of a vasodilating agent, alone or in combination with a steroid, a steroid agonist, partial agonist, or antagonist (col. 4, lines 7-11; col. 8, lines 28-35). The disclosed steroid may be an estrogen, a progesterone, or an androgenic agent; the latter taught only within the context of pharmaceutical formulations adapted for local administration (col. 4, lines 35-44 and 45-49).

The hypothetical combination of Adams et al. in view of Place et al. does not render the claimed invention obvious for the following reasons:

With respect to claim 1, Adams et al. does ***not*** teach or suggest the co-administration of an androgenic agent with anything other than the disclosed dopaminergic, serotonergic, oxytocinergic, or nitroxidergic pathway compounds. Accordingly, the following drug combinations are not contemplated within the scope of the Adams et al. disclosure: an oral androgenic agent co-administered with a rho kinase inhibitor, a melanocortin peptide, an endothelin antagonist, a growth factor, a cytokine, a selective androgen receptor modulator, a neuropeptide, an amino acid, a serotonin antagonist, a dopamine antagonist, a potassium channel opener, a potassium channel blocker, and a non-androgenic steroid. As the foregoing combinations are the subject matter of claim 1, it follows that claim 1 and all claims depending from claim 1 are not rendered rendered obvious by Adams et al. alone.

Place et al. does not correct the deficiencies of Adams et al. Place et al. teaches the local administration of a vasodilating agent as a primary active agent and the ***local*** administration of androgenic agent as a secondary active agent. Place et al. does ***not*** teach or suggest the co-

administration of either the primary vasodilator or the secondary androgen with any of the following drugs: rho kinase inhibitors, melanocortin peptides, endothelin antagonists, growth factors, cytokines, selective androgen receptor modulators, neuropeptides, amino acids, serotonin antagonists, dopamine antagonists, potassium channel openers, potassium channel blockers, and non-androgenic steroids. Accordingly, there is no teaching of Place et al. that may be imported into the teachings of Adams et al. that would enable one of ordinary skill in the art to arrive at claim 1. Thus, it follows that claim 1 and all claims depending from claim 1 are not rendered obvious by Adams et al. in view of Place et al.

With respect to claim 44, Adams et al. teaches that the potentiating influence of apomorphine in female rats was found to be maximal when testosterone is administered about 36 hours *prior to administration of apomorphine*. Based upon this observation, Adams et al. discloses that testosterone should be administered 2 to 48 hours *prior to administration of apomorphine* (page 21, lines 3-13; page 8 line 28 to page 9, line 8; Figure 2). Adams et al. does ***not*** teach administration of the androgen *prior to anticipated sexual activity* or administration of a prostaglandin *following sexual activity*. Accordingly, it is clear that Adams et al. alone does not render obvious claim 44. Place et al. does not correct the deficiencies of Adams et al. because Place et al. provides no express teaching on the timing of administration for either the local vasoactive agent or the androgenic agent disclosed therein. Accordingly, claim 44 is not rendered obvious by Adams et al. in view of Place et al.

With respect to independent claim 50, the purpose of Adams et al. is to administer a compound that acts upon mid -brain pathways to increase blood flow to the ilio-hypogastric-pudendal arterial bed and genitalia. To effectuate this purpose, Adams et al. discloses the oral administration of compounds known to act upon mid-brain pathways to increase blood flow to the ilio-hypogastric-pudendal arterial bed, namely, dopaminergic, serotonergic, oxytocinergic, or nitroxidergic pathway compounds, with apomorphine being the preferred compound. As discussed above, the androgenic agent, testosterone, is co-administered with the apomorphine for purposes of potentiating the effects of the apomorphine. Because Adams et al. does not contemplate orally administering the androgenic agent to the individual in an amount effective to provide a blood level of the agent or a metabolite thereof that approximates the blood level of the agent or a metabolite thereof during ovulation, it follows that claim 50 is not rendered obvious by Adams et al. alone. Place et al. does not correct the deficiencies of Adams et al. because Place et al. does not provide the missing teaching. Accordingly, claim 50 is not rendered obvious by the combination of Adams et al. in view of Place.

With respect to independent claims 56 and 59, Adams et al. does not teach or suggest the addition of a vasoactive agent to the apomorphine-androgenic agent combinati n. Accordingly, claims 56 and 59 are not rendered obvious by Adams et al. alone. Place et al. does not correct the deficiencies

of Adams et al. While Place et al. teaches the administration of a local vasoactive agent in combination with a local androgenic agent, it neither teaches or suggests the administration of the vasoactive agent in *oral form*. Thus, it follows that claims 56 and 59 and all claims depending from claims 56 and 59 are not rendered obvious by Adams et al. in view of Place et al.

Because the hypothetical combination of Adams et al. in view of Place et al. does not render the present invention obvious, Applicants respectfully request reconsideration and withdrawal of this rejection.

RESPONSE TO EXAMINER'S ARGUMENTS

The Examiner asserts that it would have been obvious for one of ordinary skill in the art to practice an oral androgenic agent in combination with any of the recited secondary agents for the treatment of female sexual dysfunction (Office Action, pages 5-6). Applicants respectfully submit that the Examiner's analysis is outside the boundaries of well-established patent law principles on obviousness rejections. An obviousness analysis within the context of PTO prosecution raises two related inquiries: (i) whether a combination of the teachings of all of any of the references would have suggested (expressly or by implication) the possibility of achieving further improvement by combining such teachings along the line of the invention in suit; and (ii) whether the claimed invention achieved more than a combination that any or all of the prior art references suggested, expressly or by reasonable implication. *In re Senaker*, 702 F.2d 989, 994, 217 USPQ 1 (Fed. Cir. 1983). When considering whether a references suggests an improvement, it is important to remember that the fact that a prior art teaching may be modified to produce the claimed invention is ***not*** a basis for an obviousness rejection unless the prior art ***suggested*** the desirability of the modification. *Cable Electric Products, Inc. v. Genmark*, 770 F.2d 1015, 226 USPQ 881 (Fed. Cir. 1985); *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

The foregoing analysis of the Adams et al. and Place et al. reference demonstrates that the combination of the two references in all instances lacks key elements recited in the claims of the instant application. Further, the two references in combination provide no suggestions to modify the teachings disclosed therein such that the claimed invention is rendered obvious. To wit, with independent claim 1, the cited references in combination provide no teaching or suggestion that would lead the ordinary artisan to orally administer any of the recited secondary compounds. With independent claim 44, the cited references in combination do not provide any teachings or suggestions that would lead the ordinary artisan to apply a topical prostaglandin 0.25 to 24 following sexual activity. With independent claim 50, the cited references in combination do not provide any teaching or suggestion that would lead

the ordinary artisan to apply an oral androgen in such a way that the blood level of the androgen approximates the blood level of the androgen during ovulation. With independent claims 56 and 59, the cited references provide no teachings or suggestions that would lead the ordinary artisan to administer the topical vasoactive agent of Place et al. in oral form.

Because Adams et al. and Place et al., alone or in combination, fail to suggest the modifications of the claimed invention, it follows that the claimed invention achieves more than the combined teachings and suggestions of Adams et al. in view of Place et al. In view of the foregoing, it must be concluded that the Examiner's assertion of obviousness is not supported by well-established Federal Circuit law.

CONCLUSION

With the present Amendment, all outstanding objections and rejections for the present application have been addressed. Specifically, the Examiner's claim objections are rendered moot as a result of deletion of the objected-to language from claim 1 and the obviousness rejection has been fully addressed on both factual and legal grounds. Because the foregoing amendments and remarks demonstrate that the application is free of art and in condition for allowance, applicants respectfully request withdrawal of all claim rejections, favorable action on all claims, and passage of this application to allowance.

The Examiner is invited to contact the undersigned at 650-330-4913 with questions or comments regarding this paper.

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